Epigenetics in DOHaD: discriminating cause and effect relationships.

DOHaD 研究（ISSN 2187-2597）
2017 年 第 6 巻 第 1 号 5 頁

特別講演（３）

Epigenetics in DOHaD: discriminating cause and effect relationships.

Dr Allan Sheppard

Liggins Institute, University of Auckland, New Zealand

The concept of DOHaD is finding increasing acceptance amongst clinicians and scientists. Numerous studies in human cohorts and animal models now provide both epidemiological and experimental in support of the notion that environmental cues (most significantly nutrition) experienced during pregnancy can indeed influence the future life-course of the progeny. It has often been suggested that epigenetic mechanisms might mediate these signals and provide a molecular basis for DOHaD phenomena. Variantion in the expression of epigenetic marks (most often levels of DNA methylation) is found to be strongly ***'associated' statistically*** with DOHaD outcomes.

While empirical data has demonstrated the importance of epigenetic mechanisms in influencing embryogenesis in model systems (a few examples of which will be presented), there is very little evidence that they are similarly important as ***'casual determinants'*** of DOHaD related outcomes. This is particularly true in the human context, because of the obvious ethical and technical limitations of manipulating epigenetic signals during pregnancy and development. A broader consideration of the biological origin and the 'logic' of epigenetic processes in biological systems does however encourage the view that they may indeed be causal in the manifestation of DOHaD phenomena.

Although the evolutionary appearance of epigenetic marks predates the emergence of eukaryotic cells, it is the development of tissue multi-cellularity which seems to have facilitated the increasing complexity of epigenetic processes. Thus, the functional specialization of individual cell types (which share an identical genomic inheritance) has been achieved through the differential expression of distinct epi-phenotypes, in response to critical non-genetic cues. ***The epigenome thus serves as a key interface between the environment of the organism and the 'expression' of its nuclear DNA inheritance.***

The most important environmental influence that we currently recognize is probably energy availability, given that increased biological complexity is concomitant with higher energetic demands required for both maintenance and replication. Conversion of macro- and micro-nutrients into usable forms of energy occurs through glycolysis and mitochondrial bioenergetics pathways, the rates of which determine the intracellular levels of key metabolites, notably ATP, acetyl CoA, SAM and NAD/NADH. The fluctuation of these specific energy intermediates regulates a spectrum of epigenetic processes, and thus links the nutrient supply in the organism's environment to the variable expression of nuclear DNA in cells, and consequently the manifestation of epi-phenotypes. ***Mitochondrial bioenergetics thus serves as a key interface between the environment of the organism and the epigenome.***

The endosymbiotic incorporation of mitochondria by cells during evolution was thus a pivotal stimulus for realizing the potential and diversification of epigenetic regulatory pathways. In modern eukaryotic cells an on-going dialogue between the mitochondrial and nuclear genomes (in response to environmental signals) is mediated largely by epigenetic signalling. ***The top-down chain of causality*** which thus emerges from this broader consideration begins with ***nutrient availability in the environment of the organism, which in turn determines the level of mitochondrial bioenergetics, which in turn determines the state of the epigenome in the cell and thus, the landscape of collective gene expression (epi-phenotype) measured in the cell at any given time.***

This particular perspective of epi-phenotype regulation also highlights the clearly intimate inter-dependence of bioenergetics and epigenetics, and provides a rationale for the extraordinary expansion of epigenetic mechanisms through evolution. Further, the long assumed genetic basis of many diseases is increasingly being questioned. As an alternative view, their etiology/patho-physiology are postulated to begin with mitochondrial dysfunction (a consequence of sub-optimal or markedly perturbed nutrition and metabolic states) and the impact this has on shifting the trajectories within the epi-phenotype ("Waddington") landscape. Defining DOHaD related outcomes in similar terms would not only provide mechanistic insight, but also confirm the central causal role of epigenetics in the manifestation of such phenomena.

(CV)

Senior Research Fellow Liggins Institute, University of Auckland

Academic qualifications

2008 –present Senior Research Fellow Liggins Institute, Univ of A

2005 – 2012 Senior Scientist AgResearch Limited

2003 – 2005 Assistant Research Scientist on College of Agriculture & Environmental

Faculty Science, Univ. of Georgia, Athens, GA

1998 – 2003 Biotechnology Research Fellow National Cancer Institute, National Institutes of Health, Bethesda, MD

1994 – 1998 Research Assistant Professor Department of Medicine, Washington Univ. School of Medicine, St. Louis, MO

1992 – 1994 Research Associate Department of Medicine, Washington Univ. School of Medicine, St. Louis, MO

1989 – 1992 Research Associate Department of Cell Biology,

Washington U School of Medicine

Present research/professional speciality

Developmental Epigenetics, Life History and Phenotype, Epigenetics

Developmental adaptation to an obesogenic environment

Total number of *peer reviewed* publications and patents

Peer reviewed journal articles 75 , nConference proceedings 45

Ptents 9